BioProcess Insider eBooks

# GENE THERAPIES

## DEVELOPERS SLOWLY EMERGE FROM A PANDEMIC

**Dan Stanton and Gareth Macdonald**


February 2022

# Gene Therapies

## Developers Slowly Emerge from a Pandemic

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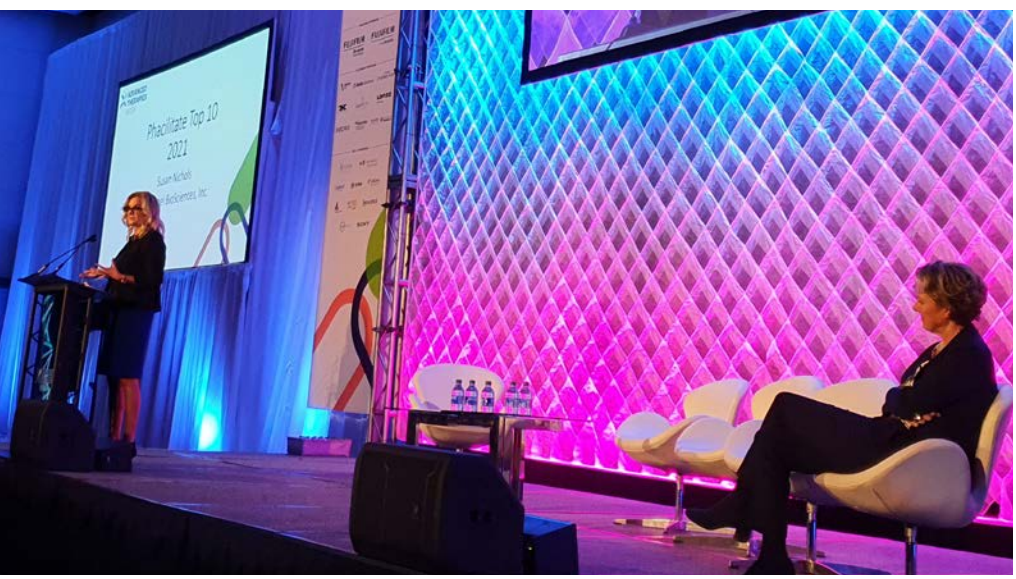


Gene-therapy developers and industry suppliers are strategizing to recover from the COVID pandemic. At the 2022 Phacilitate Advanced Therapies Week, participants reviewed the current state of investments and clinical pipelines. Discussions from FDA Advisory Committee meeting in Fall 2021 also provided insights to help prevent clinical trial failures. To advance their gene-therapy programs, Pfizer and Novartis have boosted their internal platforms and capabilities, and a 2021 BPI conference presenter emphasized the importance of high-quality analytics.

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# 2021: A Bad Year for Gene Therapies

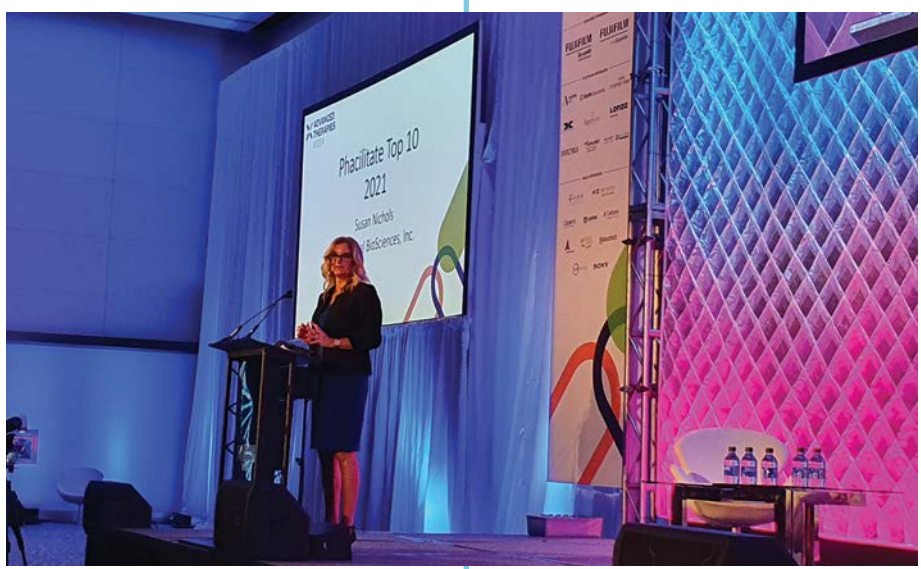
## What's Next?

**Dan Stanton**

Every January (barring global pandemic restrictions), the cell and gene-therapy industry flocks to Miami, FL, to reflect on the previous year's achievements and to look ahead to the coming year. Among the most anticipated standing presentations at Phacilitate's Advanced Therapies Week is that by Susan Nichols (CEO of Propel Biosciences), who runs through the top 10 achievements in the advanced therapy space from the previous year.

It is no surprise that the advancement of gene therapies has featured high on these lists. The approval of Spark Therapeutics's Luxturna (voretigene neparvovec) — the first directly administered gene therapy — hit the top spot in 2017 (**1**). Two years later, the May 2019 approval of Novartis–AveXis's Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy (SMA) propelled gene therapy further into the limelight, and the modality thus featured prominently in Nichols's top 10 observations of 2019 (**2, 3**). The top spot that year went to patient-access concerns, driven by Zolgensma's US $2.1 million price tag, but 2019 also saw numerous financial and deal-making movements surrounding gene therapies. With Roche's $4.3 billion acquisition of Spark, Pfizer's hefty investment in Vivet Therapeutics, and Biogen's $800 million Nightstar Therapeutics deal, Big Pharma's buying power in the sector was clearly on display (**4–6**).

Nichols noted the "somewhat impressive" arrival of large third-party manufacturers into the gene-therapy space, with Thermo Fisher's $1.7 billion acquisition of Brammer Bio and Catalent's $1.2 Paragon Bioservices purchase (**7, 8**). In-house manufacturing investments further demonstrated confidence in the sector: Novartis bolstered its network to support the Zolgensma production; Pfizer

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ramped up its internal adenoassociated virus (AAV) vector capacity with a $500 million facility investment in Sanford, NC; and Bluebird Bio opened an $80+ million facility in Durham, NC (**9, 10**).

Thus, optimism was high as industry looked to 2020 and beyond. Two years later, however, the gene-therapy sector appears to be in somewhat of a tailspin. In 2021, the industry saw U-turns in two of the above examples of in-house production expansion. Novartis off-loaded a facility in Longmont, CO, to AGC Biologics, citing a change in its Zolgensma manufacturing capacity needs, and Bluebird Bio sold the Durham lentiviral vector production site to Resilience (**11, 12**).

Those examples alone do not brood pessimism across the gene-therapy landscape. Rather, they might represent a microtrend in the space, a recalibration of end user needs, or the growing reliance on contract development and manufacturing organizations (CDMOs) for vector production. More conspicuous was a series of adverse events with AAV-based candidates over the past year placed gene therapies third on Nichols's illustrious list of major events in 2021 for all the wrong reasons.

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## Investment and Advancement: Reasons To Be Positive

In the early days of the COVID-19 pandemic, there were jitters in the biopharmaceutical industry surrounding the logistics of carrying out clinical trials and the security of viral vector manufacturing capacity. But from financing and development perspectives, "[The year] 2021 was an auspicious year for the cell and gene therapy (CGT) sector, which bodes well for the future," according to Janet Lambert (CEO of the Alliance for Regenerative Medicine, ARM). Across the entire CGT space, the industry made record-breaking investments, she told delegates at Phacilitate's Advanced Therapies Week in January 2022. Of the $23.1 billion invested, $10.6 billion was directed specifically into gene therapies, up 14% from the prior year. A significant proportion of that ($4.7 billion) was raised by companies active in gene editing.

From a commercial point of view, 2021 lacked the big-hitting FDA approvals in 2017 and 2019 for the Luxturna and Zolgensma products, respectively. Gene therapies took a back seat as chimeric antigen receptor T-cell (CAR-T) therapies took the regulatory accolades. The FDA approved Bristol Myers Squibb's Breyanzi (lisocabtagene maraleucel) and Abecma (idecabtagene vicleucel) products, and the European Commission approved Bluebird Bio's Skysona (elivaldogene autotemcel, Lenti-D) one-time gene therapy for the treatment of early cerebral adrenoleukodystrophy (CALD).

However, 2022 is shaping up to be a major year for regulatory decisions, Lambert said. The FDA expects to cast its decision on 15 advanced therapies. Of the following, almost half are potential gene therapy approvals:

- BioMarin's valoctocogene roxaparvovec for hemophilia A
- Bluebird's betibeglogene autotemcel (beti-cel) for β-thalassemia
- Bluebird's Lenti-D product for CALD
- Bluebird's lovotibeglogene autotemcel (lovo-cel) gene therapy for sickle cell disease (SCD)
- Krystal Biotech's Vyjuvek (beremagene geperpavec, B-VEC) topical gene therapy for epidermolysis Bullosa
- PTC Therapeutics's PTC-AADC product for aromatic l-amino acid decarboxylase (AADC) deficiency
- uniQure/CSL Behring's etranacogene dezaparvovec for hemophilia B

In addition to the above candidates, pipelines are bulging with potential gene therapies. According to ARM's figures (as of Q3 2021), 1,129 industry-sponsored clinical trials are being conducted across the full CGT sector. Of that total, 222 are specifically pure-play gene therapies, with 43 in phase 3, 47 in phase 2, and 132 in phase 1 trials. An additional 84 gene therapies (3 phase 3, 24 phase 2, and 57 phase 1) are part of the total 1,132 academic- and government-sponsored CGT trials.

"In 2022 and beyond, we will see a gradual evolution from [treating] rare monogenic diseases and liquid tumors to more prevalent diseases and solid tumor cancers," Lambert said. "Importantly, the first gene therapy for a prevalent disease could be just a few years away."

She referred to the now fabled prediction from former FDA Commissioner Scott Gottlieb that by 2025 the agency will be approving 10 to 20 CGT products a year (**15**). "By our estimation looking at the pipeline and what's been publicly announced, we think that's probably doable — though our guess would be that we would be at the lower end of that range."

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And the list is substantial: In September 2021, a clinical hold was placed on BioMarin's Phearless phase 1–2 trials evaluating BMN 307 — an investigational AAV5-phenylalanine hydroxylase (PAH) gene therapy in adults with phenylketonuria (PKU) — after tumor development was reported on mice in preclinical studies (**13**). In the same month, Astellas Pharma placed the clinical trial of its Aspiro gene-therapy candidate (a treatment of X-linked myotubular myopathy) on hold after the death of a clinical trial subject (**14**). That came just five months after the US Food and Drug Administation (FDA) lifted a clinical hold following earlier trial-subject deaths, which led to Astellas Pharma's switching to a lower dose of its AAV8-vector–based candidate.

Adverum Biotechnologies suffered a setback in its development of wet age-related macular degeneration gene therapy ADVM-022 after a toxicity incident left a trial subject with vision loss during a phase 2 study. In the field of Duchenne muscular dystrophy (DMD), gene therapies also struggled in 2021. Pfizer, one of the frontrunners in bringing gene therapies to market, was hit by trial setbacks. The company reported severe muscle weakness and myocarditis in subjects during trials of fordadistrogene movaparvovec, previously known as PF-06939926. In December, Pfizer announced that a phase 1b trial participant had died. Both setbacks were bad news after DMD gene-therapy rival Sarepta Therapeutics failed a phase 2 clinical trial earlier in 2021 (**16, 17**). Clinical hold and safety incidents have also marred Solid Bioscience's efforts in the DMD gene-therapy space, though the company presented positive data from its ongoing Ignite DMD phase 1–2 SGT-001 clinical trial late last year.

In December 2021, Bluebird Bio announced that the FDA placed its clinical program for lovotibeglogene autotemcel (lovo-cel) gene therapy for sickle cell disease (SCD) on partial clinical hold because of an ongoing investigation into an adolescent subject with persistent, nontransfusion-dependent anemia following treatment.

AAV-based gene therapies are known to cause hepatoxicity, thrombotic microangiopathies (TMAs), dorsal root ganglia neuronal loss, brain MRI abnormalities, and both oncogenicity and AAV vector integration across animal and human models. "To me, this indicates that we have a whole lot of learning to do with safety and dosing," Nichols's told the delegates in Miami in January. "[The approved gene therapies] Luxturna and Zolgensma benefit patients. They save lives, so what that tells us is that it can be done."

## Advisory Committee Outcomes

The numerous adverse events led regulators to take note. In September 2021, the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) sat down with industry representatives to discuss the toxicity risks of AAV-vector–based gene therapies, with a goal of providing industry best practice in its development of such modalities and recommending strategies to minimize the risk to patients.

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The FDA's formation of the advisory committee was "a useful decision because the agency has information that no individual company has, thus [providing] an important perspective for the field," Janet Lambert (CEO of the Alliance for Regenerative Medicine) said during a panel discussion on advancing AAV-based therapies.

Although no specific guidance has emerged from the meeting, participants mostly agreed that animal models are problematic for assessing AAV vector safety and that standardization in analytical characterization of AAV capsids would be an ideal to aim toward.

"One of the nice things about the [advisory committee] was that there seemed to be a collective understanding [that] there needed to be a nuanced response . . . to what had happened to avoid future painful events and to appreciate what is working in AAV," Lambert continued. "We also felt, coming out of it, [that the FDA] does not seem to lend itself to a one-size-fits-all solution for how to address [the issues we've seen with AAV] and avoid them in the future. That's difficult because we'd all like to fix these problems with a single stroke of a pen."

She added that thousands of trial subjects have been treated safely with AAV-based gene therapies. Furthermore, having two "very successful products on the market" is proof of concept — AAV gene therapies clearly can overcome their current issues.

As a marketing authorization holder for one of those "successful products," Novartis contributed to the advisory commitee meeting by sharing its experience with AAV9 thrombotic microangiopathy studies during its Zolgensma product development. Shephard Mpofu (chief medical officer at Novartis Gene Therapies) said that sharing and publishing safety data benefits the whole field. "With Zolgensma, we have had great success, having treated more than 1,600 babies worldwide. With that, we have generated a huge number of safety understandings. In addition, being on a platform where we have generated quite a number of preclinical studies — and having been a company that faced a setback in having a clinical hold on our intrathecal formulation —we have worked with the regulators to really have a comprehensive package that unravels learnings on the platform pertaining to safety (**18**). We're in a position where we will be able to publish the learnings of this comprehensive package on digoxin toxicity and biodistribution across different tissues within the field of AAV9."

For biotechnology and smaller companies, the transparency coming from the advisory committee has been instrumental in expediting projects and preventing pitfalls in AAV gene-therapy development. Tim Farries (principal consultant at regulatory consultancy firm Biopharma Excellence) added to the discussion: "On behalf of the developers, especially the small ones many with which we work, it is important to hear about these increased quality expectations as soon as possible because [developers] have to go away and implement them. They have to go away and purify

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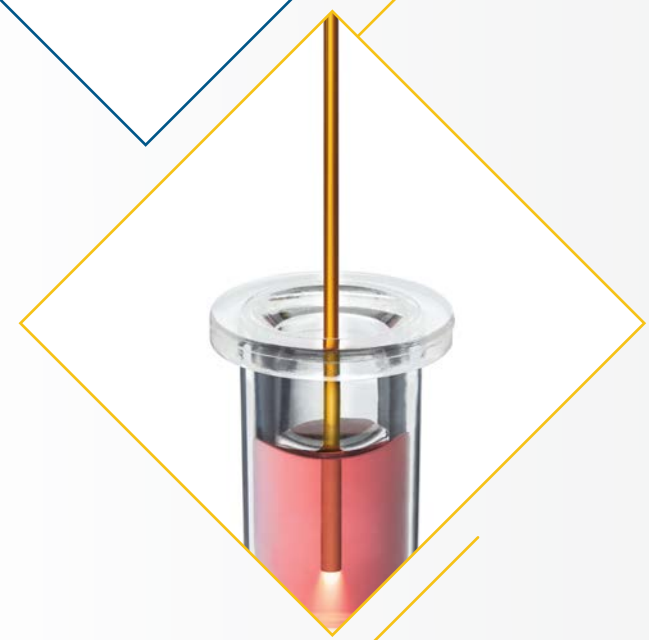

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Nichols added, "When we share all this information [with small emerging companies], they don't have to make the same mistakes that everyone made before. That will cut down the time it takes to move from drug development to clinical trials."

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## About the Author

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# Novartis Looks to Gene Therapy 3.0 to Lower CoGS

**Dan Stanton**

Swiss pharmaceutical giant Novartis is confident that manufacturing costs of gene therapies will fall as the company improves processes and brings on board next-generation technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) and other types of gene editing. The company has "always been a company that [has taken a multimodal approach] in trying to address unmet needs in a number of diseases," Shephard Mpofu (chief medical officer at Novartis Gene Therapies) said.

Shephard Mpofu was part of a fireside chat hosted by Dark Horse Consulting's Robert Allen at Advanced Therapies Week in Miami

Highlighting the company's success in small and large molecules, he reminded delegates at Phacilitate's Advanced Therapies Week in Miami, FL, that Novartis is one of the pioneers in the cell and gene therapy space. The company achieved US success for the first chimeric antigen receptor T-cell (CAR-T) therapy — Kymriah (tisagenlecleucel) — in 2017 and, through a US $8.7 billion acquisition of AveXis (**1**), won approval for its spinal muscular atrophy (SMA) gene therapy Zolgensma (onasemnogene abeparvovec) in 2019 (**2**).

Mpofu referred to the adenoassociated virus (AAV)-based Zolgensma product as "gene therapy 1.0." The company's pipeline is shifting to developing more advanced products, representing "the emergence of 2.0." By focusing on "targeted AAVs that have better affinity for the cell types in the respective indication," the company can understand fully the benefits and risks to deliver "the right amount of dose to the right target with less off-target effect."

Novartis also is looking at the next generation of gene therapies. "[Gene therapy] 3.0 factors in all the new technologies that are currently being discussed at this conference in terms of CRISPR and gene editing. And we have all this in our arsenal."

Mpofu cited recent collaborations and acquisitions as evidence of Novartis's leadership in the sector, specifically the acquisition of Vedere Bio in 2020 (**3**), adding ocular gene therapy candidates and an AAV-based delivery technology, and the more recent $800 million addition of Gyroscope Therapeutics (**4**).

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## Reducing CoGS

For Novartis, bringing a single-dose gene therapy to market was a major breakthrough, but much focus was on the Zolgensma product's $2.1 million price, driven by the high cost of goods sold (CoGS). "In terms of manufacturing, everyone understands [that] this has been one of the bottlenecks of advanced therapies because it is very complex, very individually focused," he said. He added that many elements are necessary for ensuring robust quality, scaling, and sustainability. Mpofu explained that by continuing to invest and innovate in gene therapy, Novartis continually improves its processes, and such improved efficiencies will reduce CoGS and increase patient access. However, he reminded the audience that it remains critical to "untangle the manufacturing cost from the value of the therapy," before calling for a paradigm shift in the healthcare-funding model.

"We started very early in building and understanding the holistic value of the therapy to the patient, to the caregiver, to the family, to the society, and to the healthcare system," he said. "We have a team of experts that builds models and understand the value of a [gene] therapy. Remember, this is a one-time therapy that gives a lifetime of benefit. That is almost a 21st century medicine founded in a 20th century healthcare system for chronic diseases. What we've been doing is really getting into collaborations and discussions with multiple stakeholders to understand the value of the therapy and get the best value."

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# Internal Capabilities Are the "Backbone" of Pfizer's Gene-Therapy Strategy

**Dan Stanton**

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Big Pharma companies Roche and Novartis (through the acquisitions of AveXis and Spark, respectively), have achieved regulatory success in the gene-therapy sector. Pfizer hopes to make similar achievements in the coming months and years.

To get there, the company is following a "three-pronged strategy," according to Robert Smith (senior vice president of Pfizer's global gene therapy business). This approach involves the "building of internal capabilities, complemented with selected acquisitions and an extensive network of partnerships."

Pfizer became a major player in the gene-therapy space through a number of partnerships and deals in the sector over the past five years. The acquisition of Bamboo Therapeutics in 2016 brought what is now a phase-3 gene-therapy candidate for Duchenne muscular dystrophy (DMD), and a partnership with Sangamo Therapeutics aims to bring hemophilia gene therapies to the market (**1, 2**). An agreement in 2020 sees Pfizer making supplies of VTX-801, Vivet Therapeutics' candidate gene therapy for the liver condition Wilson disease, with Pfizer having an option to acquire Vivet after the delivery of certain data from the phase 1–2 clinical trial (**3**).

But such deals are reliant on the heavy investment Pfizer has made in its internal manufacturing capabilities, Smith said at the Evercore ISI HealthCONx Virtual Conference in December 2021.

The company has three dedicated gene therapy facilities located in Morrisville, Durham, and Sanford – all in North Carolina. The Sanford site has gained a $500 million investment, announced in August 2019, Smith confirmed (**4**). "In Stanford, North Carolina (which was a biologics campus for manufacturing), we have two facilities, one of which is for both late-stage clinical and commercial manufacturing. And we have a second more expansive facility . . . with [good manufacturing practice] GMP production this month."

Smith added, "We feel confident that with the portfolio [and] the capabilities that we build, we'll be able to efficiently advance these programs into the clinic and potentially even to the market."

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# High-Quality Gene Therapies Require High-Quality Analytics

**Gareth Macdonald**

Lyndi Rice (head of the viral vector quality control analytical group at BioMarin Pharmaceutical) told delegates at the BioProcess International Conference and Exhibition in September 2021 that "analytics are really critical from the start of the manufacturing process to the end of product testing and monitoring." She added, "Release testing is critical for measuring product quality by assessing its identity strength, purity, and safety. Stability methods measure the stability of a product under different conditions and over time and can help to inform [you about the] shelf life for your product."

The key to an effective analytics strategy is to ensure that the correct methods are used at each part of the development and production process, Rice said. "It is important to ensure that the method performs as well as needed to monitor the manufacturing process at each of those steps."

Rice emphasized that information needs to be gathered at all stages of production. "It's important to collect data, especially early on in product development. These results can be leveraged during investigations to understand how product quality might have been affected [had there been] anything that maybe was a little bit off during the manufacturing process."

## Analysis "Suite" Spot

Incorporating analytical systems into process development and manufacturing facility design is the ideal approach because it can ensure that desired critical quality attributes can be monitored effectively. However, companies also need to consider the use of alternative methods according to Rice, who urged gene-therapy manufacturers to ensure a degree of flexibility in process and facility design.

"It is very important to thoughtfully design your analytical suites to be sure that they're measuring such attributes appropriately. Orthogonal approaches also might be required to measure some of those attributes."

## Consistency

Gene therapies have complex mechanisms of action, and it is crucial that developers make sure that therapeutic impact is a result of the products itself rather than a variation occurring

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during the manufacturing processes. Analytical technologies are key to minimizing batch-to-batch variation and ensuring that gene therapies are consistent, Rice said.

"Robust analytical methods are therefore required for sufficient product characterization. And you can consider during product development phase-appropriate analytical method development. So by phase 3 pivotal trials, it is expected that you would have all of your methods validated."

## Platform Process?

Selecting the appropriate analytic method and ensuring it is that provides the information needed at each stage of the process is important Rice said. "You can refine your methods as product knowledge increases and focus on method robustness, accuracy, and precision early, especially for your critical methods such as [those for assessing] dosing and potency. That is because you're going to be making important decisions based on method performance and method results. So you should focus on these methods early on in product development. Platform methods also can save time and resources without sacrificing quality, but such analytical methods do require that your manufacturing process be somewhat platform."

For gene therapies manufactured using highly technical processes, such platform-focused approaches might not be as effective. In such circumstances, companies should consider a quality-by-design approach for analytical method development.

## About the Author

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